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Mitotic Count in Seminomas – an Unreliable Criterion for Distinguishing Between Classical and Anaplastic Types

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Summary. Testicular seminomas occur in various forms of which the classical, the spermatocytic, and that with syncytiotrophoblastic giant cells are distinctly defined. Anaplastic seminomas, however, are less clearly distinguished. Forty-five seminomas, 39 pure and 6 combined tumors, were examined from the perspective of the current definition that 3 or more mitoses per high power field (m/hpf) distinguish the anaplastic from the classical form. Our resultant yield of over 80% of "anaplastic" seminomas is clearly incompatible with general clinical experience, indicating that the arbitrary criterion of 3 m/hpf does not segregate anaplastic forms from neoplasms that are mitotically active but relatively non-aggressive. Moreover, the evidence indicates that mitotic activity does not adequately define a tumor form that is near the undifferentiated end of the spectrum which extends from "embryonal carcinoma" to the spermatocytic type. If it should prove, however, that the mitotic rate must be used as an arbitrary watershed criterion until a more reliable one is found, it should then be set at more than 5 m/hpf, yielding a percentage of anaplastic seminomas (about 9%) that is compatible with clinical experience.

Key words: Seminoma – Anaplastic seminoma – Mitotic count – Embryonal carcinomatous seminoma.

Introduction

Testicular seminomas are commonly categorized into classical or typical, spermatocytic, and anaplastic. Recently, classical seminomas with additional scattered syncytiotrophoblastic giant cells have been recognized as a separate entity (Kurman et al. 1977; Javadpour et al. 1978; Hedinger et al. 1979). While the spermatocytic type presents little difficulty in recognition as a rule, the anaplastic

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is less readily distinguishable from the classical type. Nevertheless, anaplastic seminomas have been treated as a separate clinical entity by several authors (Maier and Sulak 1973; Johnson et al. 1975; Kademian et al. 1977), particularly on the basis of clinical response to treatment and allegedly worse prognosis. The morphological distinction between classical and anaplastic seminomas has not been resolved satisfactorily, however (Thackray and Crane 1976). Electron microscopic investigations have also failed to provide clear grounds for their separation (Pierce 1966; Janssen and Johnston 1978).

The light microscopic feature of elevated mitotic activity has recently gained support in helping to define as "anaplastic" an otherwise typical seminoma. Mostofi (1973) considers it "the single most important, easily recognizable and reliable feature". More precisely, three or more mitotic figures per high power field (m/hpf) are considered to manifest anaplasia (Mostofi 1973; Mostofi and Price 1973; Mostofi and Sobin 1977), although the foundation of the criterion of distinction was never substantiated, nor the area of a high power field accurately defined.

The present paper examines whether the apparently arbitrary choice of 3 m/hpf is justified as the critical point in the distinction of anaplastic from classical seminomas.

Material and Methods

Of 99 testicular germ cell tumors examined from 1975 to the end of 1977 at the Institute of Pathology of the University of Zurich, 48 (48.5%) were classified as pure classical seminomas and 14 (14.1%) as combined tumors, i.e., neoplasms uniting a seminoma with another germ cell tumor. In 17 cases of these two groups, the seminoma was either not represented in sufficient bulk or lacked adequate cytological detail to allow more than an overall diagnosis.

The remaining 39 pure seminomas and 6 combined tumors were examined separately. Haematoxylin and eosin slides from an average of 3–4 suitable paraffin blocks of the tumor bulk were evaluated in each case. From each slide, three high power fields in both central and marginal zones were selected in a way such that as little stroma as possible occupied the visual field. In this manner, uniformity in the density of seminoma parenchyma was preserved. Using a Carl Zeiss microscope with ocular and objective magnifications of $\times 10$ and $\times 40$ respectively, the field area was calculated to occupy 0.152 mm^2. All examined fields were scanned visually and mitoses counted. Care was taken to register cells involved in obvious phases of mitosis only. Other forms featuring dispersed clumping or irregular fragmentation of chromatin were not considered, as they might represent regressive alterations, karyorrhexis or other non-mitotic processes.

Results

The distinct overall impression gained from our analysis of 45 seminomatous tumors is that mitoses are frequent (Fig. 1) and quite heterogeneously distributed. The frequency of their occurrence, moreover, showed no relation to marginal or central zones.

The segregation of each of the tumor groups, i.e. pure and combined seminomas, into those with less than 3 m/hpf and those with 3 or more m/hpf is given in Table 1. In the pure seminomas alone, 34 (87.2%) had relatively elevated mitotic rates as did 5 cases (83.3%) of combined tumors. All cases considered, 86.7% revealed a mitotic activity sufficiently elevated to be designated as anaplastic, according to the current definition.

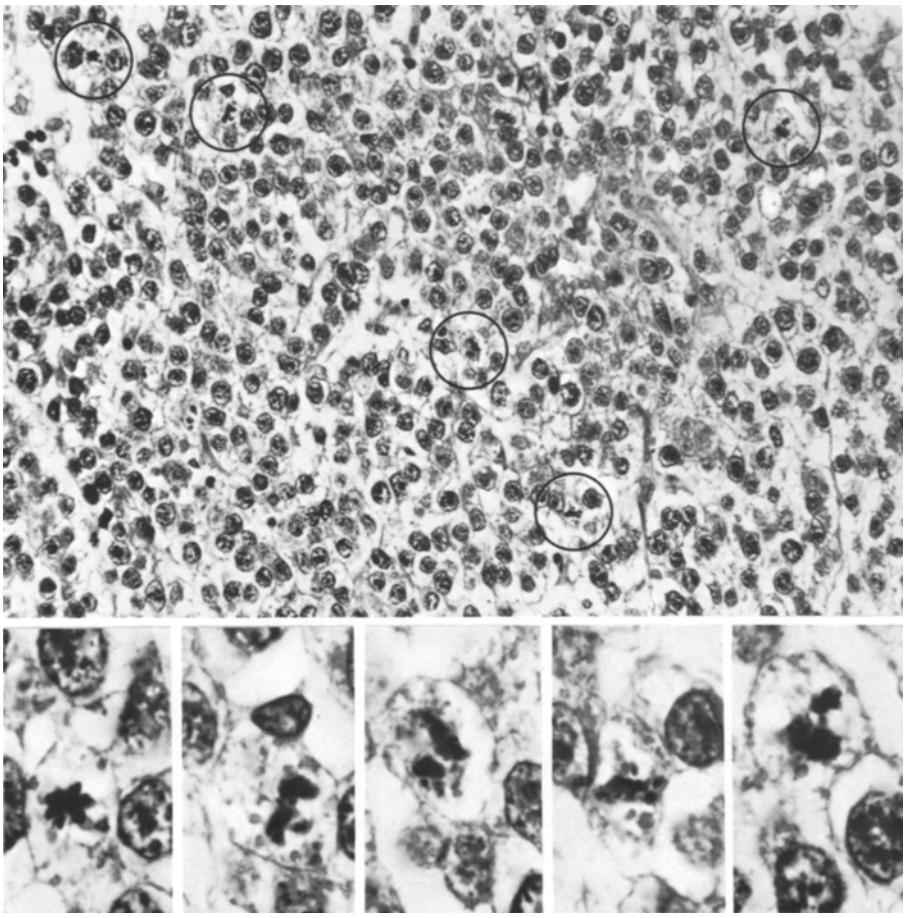

Fig. 1. Classical seminoma. The tumor parenchyma shown covers 0.129 mm^2, an area slightly smaller than a microscopic high power field (0.152 mm^2). Five mitoses (*circles*), magnified below, indicate an appreciable mitotic activity. (Magnification ×250; Insets ×1,000)

Table 1. Segregation of seminomatous tumors based on a mitotic activity of 3 m/hpf

	Total cases	Mitoses			
		Less than 3 m/hpf		3 or more m/hpf	
		N	%	*N*	%
Seminomas	39	5	12.8	34	87.2
Combined tumors	6	1	16.7	5	83.3
Both groups	45	6	13.3	39	86.7

Table 2. Segregation of seminomatous tumors based on a mitotic activity of 6 m/hpf

	Total cases	Mitoses			
		Less than 6 m/hpf		6 or more m/hpf	
		N	%	*N*	%
Seminomas	39	35	89.7	4	10.3
Combined tumors	6	6	100	0	0
Both groups	45	41	91.1	4	8.9

Elevating the criterion of segregation between classical and anaplastic seminomas arbitrarily to 6 m/hpf yielded the results shown in Table 2. In the group of pure seminomas, only 4 (10.3%) displayed 6 or more m/hpf, while among the combined tumors none had similarly elevated mitotic rates. In both groups, therefore, 4 cases (8.9%) revealed a mitotic activity such that their designation as anaplastic was justified by the newly and arbitrarily chosen definition.

Discussion

It is surprising that there is as little controversy in the literature about the morphological criteria adequately defining anaplastic seminomas as there is about the 3–10% cited in relation to their incidence (Mostofi and Price 1973; Thackray and Crane 1976). Nevertheless, when Thackray and Crane write that 23% of their seminomas were classified as poorly differentiated according to cytological and histological grading, that mitoses were numerous in 5%, but that only 3% were atypical in providing a poorer prognosis, the problem of morphological identification becomes apparent. Using the generally accepted criterion of 3 or more m/hpf to distinguish anaplastic seminomas, our incidence of over 80% is clearly incompatible not only with the figures given above, but also with our own experience in the clinical course of these neoplasms. By raising the critical mitotic rate arbitrarily to 6 m/hpf we obtain a more compatible 10.3% of pure seminomas with high mitotic activity (Table 2). Interestingly, Wurster (1976) found more than 5 m/hpf in 11% of a series of 56 classical seminomas.

In a concurrent survey, our incidences of the various groups and subgroups of testicular tumors are quite comparable to those of larger series, save minor incongruencies stemming from differences of definitions inherent in the systems of classification. In particular, our incidences of classical seminomas and embryonal carcinomas, or undifferentiated malignant teratomas (MTU) are comparable to those of larger series, indicating that embryonal carcinomas (MTU) were not mistakenly grouped with seminomas, thereby raising the overall mitotic count (von Hochstetter and Hedinger, in press).

In recent years, attention has been drawn to lesions found in close vicinity to non-seminomatous germ cell tumors, varying in appearance from atypical spermatogonia to intratubular or even frank seminoma (Skakkebaek 1975; Sigg and Hedinger 1980). Experience has shown that such "reactive neoplasms", as one might be tempted to consider them, do not clinically behave in an aggressive fashion, since they hardly, if ever, metastasize as seminomas (Pugh 1976). From our results the current definition of anaplasia in seminomatous tumors, does not do justice to this fact, however, since it does not significantly distinguish between seminomatous components of combined tumors and pure seminomas (Table 1). When the watershed criterion is raised to 6 m/hpf, however, a segregation of the two groups becomes apparent (Table 2), supporting our contention that seminomas are generally mitotically active and that a mitotic rate of 3 m/hpf lies below that threshold which might conceivably indicate differences in biological behaviour.

The practice of inferring biological behaviour from mitotic activity relies on several assumptions, the most basic being that the two are directly related. In general tumor pathology distinct exceptions are well known and paucity or abundance of visible mitoses do not always nor necessarily correlate with a benign or malignant clinical course. The practice of equating aggressive behaviour with mitotic activity neglects a constellation of variables that influence the number of microscopically detectable mitoses. The fact that cells engaged in the mitotic process may pursue it to completion before the fixative reaches them was taken into consideration by examining marginal and central areas. The overall large variation in mitotic rates, however, overshadowed any regional differences that might be present. Nevertheless, the rapidity of fixation unquestionably alters the quality of cytological detail, a factor that, along with other variables in laboratory procedure, must be responsible at least in part for significant variations in mitotic counts.

Clinical investigations have shown that anaplastic seminomas, though more aggressive in reaching advanced stages of spread and involvement, have a prognosis quite similar to that of classical seminomas when staging is taken into account (Maier et al. 1968; Johnson et al. 1975). Such clinically aggressive behaviour may be explained by earlier spread of a tumor that is at the same time no less radiosensitive than the classical seminoma. The morphological substrate for early spread may well reside in tumor growth attributes other than mitotic activity, such as vascular channel invasion (Johnson et al. 1975) or reduced cellular cohesion.

The common observation in light microscopy that occasional seminomas resemble embryonal carcinomas (MTU) or vice versa, suggests a histogenetic relationship closer than has been generally suspected (Teilum 1944; Friedman and Moore 1946; Dixon and Moore 1952; Melicow 1940; Mostofi 1973). In anaplastic germinomas, Friedman even considers the possibility of "embryonal carcinomatous transformation" (Friedman, in Skinner 1978). While electron microscopic appearances have failed to distinguish classical from anaplastic seminomas (Janssen and Johnston 1978), ultrastructural studies have repeatedly demonstrated cells of varying degrees of differentiation of which the least differentiated are often indistinguishable from those of embryonal carcinomas (MTU)

(Tomoyoshi 1962; Pierce 1966; Holstein and Körner 1974). Consequently, it seems a reasonable working hypothesis that 1) seminomas present along a spectrum of differentiation extending from embryonal carcinomatous forms to the spermatocytic; that 2) so-called anaplastic forms are found near the undifferentiated, embryonal carcinomatous end of the spectrum; and that 3) anaplastic forms differ, not so much in increased mitotic activity, as in a greater population of undifferentiated cell types.

In conclusion, the mitotic rate as observed in paraffin sections does not alone define the nature of seminomas. The arbitrary criterion of 3 m/hpf yields too high an incidence of "anaplastic" seminomas in our series and does injustice to a neoplasm that is generally mitotically active, yet behaves aggressively in a relatively small percentage of cases. If mitotic activity continues to be used in separating anaplastic from classical seminomas until more adequate criteria of distinction are found, the critical threshold should be elevated. At 6 m/hpf, the incidence of anaplastic seminomas becomes compatible with clinical experience. Questions concerning the nature of anaplastic seminomas will be resolved satisfactorily, however, only through comprehensive clinicopathological studies and quantitative ultrastructural surveys, matching biological behaviour with diverse morphological criteria of which the mitotic rate is one.

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